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Strain-Driven Dyotropic Rearrangement: A Unified Ring-Expansion Approach to α-Methylene-γ-butyrolactones

Xiaoqiang Lei, Yuanhe Li, Yang Lai, Shengkun Hu, Chen Qi, Gelin Wang, and Yefeng Tang**

Abstract: An unprecedented strain-driven dyotropic rearrangement of α-methylene-β-lactones has been realized, which enables the efficient access of a wide range of α-methylene-γ-butyrolactones displaying remarkable structural diversity. Several appealing features of the reaction, including excellent efficiency, high stereospecificity, predictable chemoselectivity and broad substrate scope, render it a powerful tool for the synthesis of MBL-containing molecules of either natural or synthetic origin. Both experimental and computational evidences suggest that the new variant of dyotropic rearrangements proceed in a dualistic pattern: while an asynchronous concerted mechanism most likely accounts for the reactions featuring hydrogen migration, a stepwise process involving a phenonium ion intermediate is favored in the cases of aryl migration. The great synthetic potential of the title reaction is exemplified by its application to the efficient construction of several natural products and relevant scaffolds.

Introduction

α-Methylene-γ-butyrolactones (MBL) represents an extremely important structural elements in bioactive natural products and pharmaceutics.[1] So far, more than 5000 MBL-containing natural products have been identified,[1c] many of which display significant biological profiles and appealing pharmacological potential. For examples, arglabin, a tricyclic sesquiterpene lactone, has been approved as a drug in Kazakhstan for the treatment of breast, colon, ovarian and lung cancers;[2] parthenolide, a small molecule that can selectively kill cancer stem cells, is now being investigated in clinical trials for the treatment of acute myelocytic leukemia and chronic lymphocytic leukemia (Figure 1).[3] Besides, MBL has also been utilized as a key pharmacophore in myriad pharmaceutical agents[4] and chemical probes[5] of synthetic origin. Interestingly, while MBL-containing compounds exhibit diverse molecular architectures, they generally exert biological functions through a similar mode, in which the MBL unit reacts with biological target through Michael addition, and thus results in the disruption of certain biological processes within the cells.[6]

Owing to its great importance, tremendous effort has been devoted to developing new methods for synthesis of MBL and related scaffolds.[1,7] Although the existing synthetic toolkits

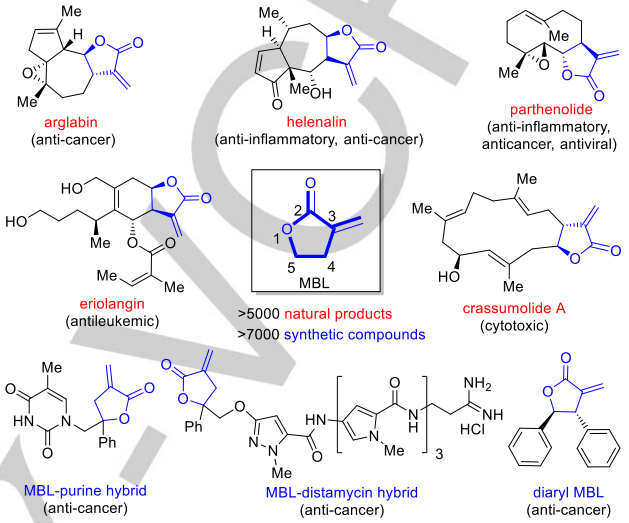

Figure 1. Representative bioactive MBL-containing compounds.

appear versatile, they are not without limitation. Firstly, most of them only permit access to MBL with limited structural diversity, especially for the substituent patterns at C-4 and C-5 positions. Secondly, with a few exceptions, they are incapable of arranging these substituents in a regio- and stereo-chemically defined manner. Thirdly, most of the known methods are built on cyclization- and cycloaddition-type reactions, and rearrangement reactions have rarely been utilized for this purpose.

Defined by Reetz in the early 1970s,[8] dyotropic reactions represent a unique class of pericyclic reactions that have attracted considerable interest from synthetic community.[9] Historically, various dyotropic reactions have been developed, among which Lewis acid-promoted dyotropic rearrangement of β-lactones is particularly notable for its appealing synthetic potential. First discovered by Mulzer and Brüntrup in 1979,[10] this type of transformations has been investigated intermittently by the Black,[11] Reetz,[12] Cossío,[13] and Romo[14] groups over the past decades. A variety of β-lactones bearing different substitution patterns have been proven to be amenable for this reaction. With a few exceptions, most dyotropic rearrangements of β-lactones proceeds through a concerted mechanism featuring a well-defined transition state (**TS,** Figure 1a), in which the adjacent C4-O1 and C5-R1 bonds disposed in an anti-coplanar alignment interchange their positions simultaneously, leading to the ring-expansion products in a stereospecific manner. Despite a seemingly attractive method to access multi-substituted γ-butyrolactones, the synthetic potential of dyotropic rearrangement of β-lactones has been largely underdeveloped, particularly in the field of nature product synthesis.[9b] This, in part, could be attributed to the difficulty in predicting and controlling the reaction outcomes, which are usually determined by the mutual interaction of the inherent steric and electronic factors associated with the reactions.

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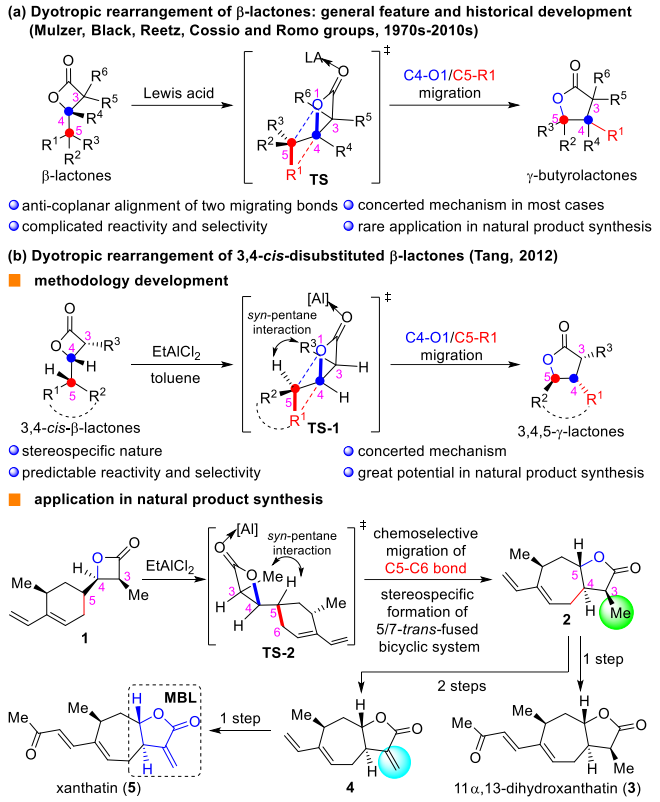


Scheme 1. Historical development of dyotropic rearrangement of β-lactones.

We have shown keen interest in dyotropic rearrangement of β-lactones over the past several years, motivated by the objective to unveil its underlying potential in natural product synthesis. In 2012, we reported a unique dyotropic rearrangement using 3,4-*cis*-disubstituted β-lactones as substrates.[15] In this work, the prearrangement of C-3 and C-4 substituents in a *cis*-configuration is crucial for securing high chemo- and stereoselectivity. Since in this scenario, a well-defined transition state (**TS-1**) with C5-H directed towards R^3 substitute should be adopted to minimize the underlying *syn*-pentane interaction (Figure 1b). As a result, only the C5-R1 bond that displays an anti-coplanar alignment with the C4-O1 bond could engage in migration, leading to the corresponding 3,4,5-trisubstituted γ–butyrolactones in a highly chemoselective and stereospecific manner. Hinging on this reaction, we completed the collective syntheses of a series of sesquiterpene lactones, namely, xanthanolides.[15,16] Of note, while this reaction is ideally suitable for the synthesis of xanthanolides bearing three contiguous stereogenic centers at the C3-C5 positions (e.g. **3**), extra functionality interconversion (Me → $=CH_2$) has to be implemented to access some other congeners featuring a MBL moiety, such as xanthatin (**5**).

Apparently, from a synthetic perspective, the more redox- and step-economy approach to access xanthatin-like natural products should hinge on the dyotropic rearrangement outlined in Figure 2, which entails α-methylene-β-lactone **6** as substrate. However, we noticed that this variant of dyotropic rearrangement had never been explored before, which indicated it might be much more challenging than expectation. It is likely that a small structural change at the C-3 position of β-lactone may notably change its reactivity and selectivity in dyotropic reaction. On one hand, α-methylene-β-lactone displays a higher ring-strain energy (RSE) than those conventional β-lactones,[17] and thus it is more easily

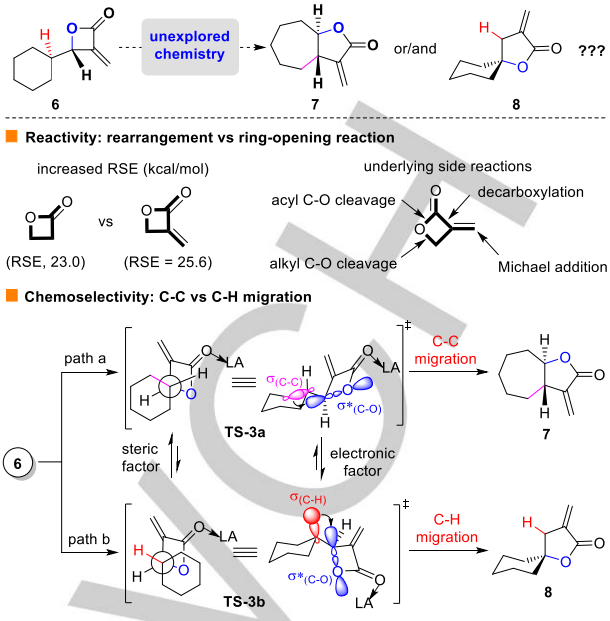


Figure 2. Original ideal and rationalization.

to undergo various ring-opening reactions. Indeed, alkyl C-O bond cleavage was documented as a side reaction in the previous dyotropic rearrangement of β-lactones.[10b,18] We anticipated that such tendency might be further enhanced in the current case because of the increased RSE and the involvement of a stabilized allylic carbocation intermediate. One the other hand, as a densely functionalized small ring system, α-methylene-β-lactone could also engage in other transformations such as acyl C-O cleavage,[19] Michael addition,[20] and decarboxylation reaction.[21] In this context, it would be challenging to achieve the expected dyotropic rearrangement without the interference of underlying side reactions. Beside reactivity issue, the selectivity of the reaction also appeared uncertain. Taking α-methylene-β-lactone **6** as example, it could undergo dyotropic rearrangement through either C-C or C-H bond migration. A simple analysis of the conformations of transition states **TS-3a** and **TS-3b** suggested that the former showed less steric effect, and thus the pathway leading to the 5/7-*trans* bicyclic compound **7** (path a) might be favored if only considering the steric factor. However, distinct from 3,4-*cis*-disubstituted β-lactone, α-methylene-β-lactone possesses more conformational flexibility, and thus steric factor may not play a determining role in the current case. This hypothesis is supported by our calculation study, which shows that the energy differences between the conformations of **TS-3a** and **TS-3b** are trivial (for details, see SI), indicating that both of them might be adopted in practice. Since the σ orbital for C-H bond generally has a higher energy than that of C-C bond, and a stronger orbital overlap between the σ (C5-H) and σ*(C4-O1) could be conceived for **TS-3b**. Therefore, it is likely that C-H migration would take place preferentially in practice, resulting in the 5/6-spiro bicyclic compound **8** as a major product (path b).

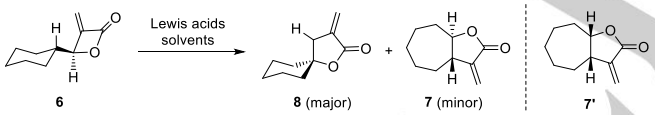
Keeping the above rationalization in mind, we initiated a program to explore the new variant of dyotropic rearrangement. Rewardingly, we finally succeeded in the development of a mechanistically interesting and practically useful dyotropic rearrangement of α-methylene-β-lactones, which holds a great promise to serve as an enabling tool in organic synthesis and biomedical research.

10.1002/anie.202013169

Results and Discussion

Condition Optimization. In a line with our previous work,[15] the designed dyotropic rearrangement of α-methylene-β-lactone **6**[19] was first conducted in toluene with Et_2AlCl as promoter. The starting material was quickly consumed, resulting in only one isolated product in 34% yield, which was determined to be 6/5-spiro bicyclic MBL **8** (entry 1, Table 1). Careful analysis of the ^1H NMR spectrum of **8** indicated that it was contaminated with a trace amount of 5/7-*trans*-fused bicyclic MBL **7** (**8:7** > 20:1).[22] The preliminary outcome, albeit failed to afford the originally proposed 5/7-bicyclic MBL relevant to our natural target, proved that α-methylene-β-lactones could serve as suitable substrate for dyotropic rearrangement. Encouraged by this discovery, we continued to conduct a systematic condition optimization, with the aim to develop the new variant of dyotropic reaction into an enabling tools for the synthesis of MBL-containing compounds. Various Lewis acids were evaluated first, which revealed that they exerted a profound influence on the reaction outcomes. Among the aluminum-based Lewis acids (Et_2AlCl, $EtAlCl_2$ and $AlCl_3$) (entries 1-3), $EtAlCl_2$ and $AlCl_3$ afforded notably improved yields (70% and 50%) than Et_2AlCl, suggesting that an increase of Lewis acidity is beneficial to reaction efficiency. However, in both cases the chemoselectivity decreased. Indeed, we could even detect a trace amount of 5/7-*cis*-bicyclic product (**7′**) in these cases. To obtain an ideal balance between the efficiency and selectivity, we further evaluated several other Lewis acids including $TiCl_4$, $MgBr_2{\cdot}Et_2O$, and $BF_3{\cdot}Et_2O$ (entries 4-6). Among them, $MgBr_2{\cdot}Et_2O$ gave the best selectivity by affording **8** as a single product in an acceptable yield. Next, a variety of solvents were explored with $EtAlCl_2$ as promoter (entries 7-12), among which the best yield (71%) and selectivity (20:1) was obtained with Et_2O. Furthermore, increasing the reaction concentration could notably shorten the reaction time without compromise of efficiency and selectivity

Table 1 Condition optimization of dyotropic rearrangement of α-methylene-β-lactone[a]



6 8 (major) 7 (minor) 7′

Entry	Lewis acid	Solvent	c (mol.L^{-1})	Time	Yield (%)[b] (**8:7**)[c]
1	Et_2AlCl	Toluene	0.025	15 min	34 (>20:1)
2	$EtAlCl_2$	Toluene	0.025	1 min	70 (19:1)[d]
3	$AlCl_3$	Toluene	0.025	3 min	50 (5:1)[d]
4	$TiCl_4$	Toluene	0.025	1 min	62 (>20:1)
5	$MgBr_2{\cdot}Et_2O$	Toluene	0.025	10 min	51
6	$BF_3{\cdot}Et_2O$	Toluene	0.025	36 h	14 (>20:1)
7	$EtAlCl_2$	CH_2Cl_2	0.025	1 min	69 (9:1)
8	$EtAlCl_2$	Mesitylene	0.025	1 min	64 (>20:1)[d]
9	$EtAlCl_2$	Benzene	0.025	1 min	60 (9:1)[d]
10	$EtAlCl_2$	C_6F_6	0.025	1 min	68 (>20:1)[d]
11	$EtAlCl_2$	*p*-xylene	0.025	1 min	64 (>20:1)[d]
12	$EtAlCl_2$	Et_2O	0.025	90 min	71 (>20:1)
13	$EtAlCl_2$	Et_2O	0.05	20 min	74 (>20:1)
14	$MgBr_2{\cdot}Et_2O$	Et_2O	0.05	5 min	63

[a]Reaction conditions: **6** (0.20 mmol), 1.1 equiv Lewis acid. [b]Isolated yield. [c]Determined by ^1H NMR. [d]With a trace amount of **7′** detected.

(entry 13). Finally, it was found that the combination of $MgBr_2{\bullet}Et_2O/Et_2O$ could also serve as an alternative choice of optimal conditions, which delivered **8** as the sole product in an acceptable yield (63%) (entry 14).

Substrate Scope. Having the optimal conditions in hand, we turned to evaluate the substrate scope. Initially, the structural variants at C-5 position were explored extensively. Based on the substituent patterns, all of the examined α-methylene-β-lactones were classified into five groups (Figure 3). For type I substrates that bear two alkyls and one hydrogen on the C-5 position, all reactions underwent C-H migration exclusively, delivering 5,5-dialkyl-substituted BML (**9**-**24**) in satisfactory yields. Several 5/6-spiro bicyclic MBL (**9**-**11**) were prepared by this method with high diastereoselectivity, among which **10** was unambiguously confirmed by the X-ray crystallographic study.[23] For α-methylene-β-lactones bearing two different alkyls ($R^1 \neq R^2$), a pair of diastereoisomeric precursors (ca. 1:1 ratio) were used directly, as they eventually resulted in identical products (**14**-**21**) after migration. Two natural product-derived BML **23** and **24** were also prepared through this reaction, suggesting that it can serve as an enabling tool for late-stage modification of natural products.

For α-methylene-β-lactones carrying one aryl, one alkyl and one hydrogen at C-5 position, the substrates were divided into two categories: type II with C5-C(aryl) and C4-O1 bonds aligned in an *anti*-configuration and type III with the opposite *syn*-configuration. Gratifyingly, both types of substrates proved to be amenable for dyotropic reaction by delivering the corresponding products (**25**-**70**) in excellent yields. Several features of these reactions deserve further discussion. Firstly, in all examined reactions, aryl migration took place exclusively, giving rise to 4-aryl-5-alkyl-MBL as the sole regioisomer. This result suggests that aryl has a greater migratory priority than both hydrogen and alkyl. Secondly, all of the reactions proceeded in a stereospecific manner, with 4,5-*anti*- and 4,5-*syn*-α-methylene-β-lactones leading to 4,5-*trans*- (**25**-**47**) and 4,5-*cis*-substitued BML (**48**-**70**), respectively. This finding shows that the stereochemistry of substrates could perfectly transfer to products via stereospecific dyotropic rearrangements, which renders the reaction predictable and controllable. Thirdly, diverse functionalities (e.g. alkene, alkyne, halides, oxygen- and sulfur ether) were tolerated in the reactions, which paves the way for further derivatization upon needed.

Not surprisingly, for 5,5-diaryl-α-methylene-β-lactones (type IV), aryl migration also took place exclusively, resulting in 4,5-diaryl-substituted MBL. However, the chemoselectivity and stereochemical outcomes turned out to be more complicated than the aforementioned cases, largely depending on the interplay of inherent electronic and steric factors. For example, for α-methylene-β-lactones bearing two identical aryls ($Ar^1 = Ar^2$), 4,5-*trans*-diaryl-substituted MBL (**71**-**75**) were obtained as the single diastereoisomers. That means although the two aryls have same electronic property, one of the diastereotopic groups (Ar^1) is easier to migrate than the other (Ar^2) due to the favorable steric effect associated with its corresponding transition state, in which Ar^2 was arranged far away from the β-lactone ring. The situation becomes even intricate when two aryls are different ($Ar^1 \neq Ar^2$), since these substrates were only accessed as a pair of inseparable diastereoisomers (1:1 ratio), both of which could undergo dyotropic reactions. Generally, when the two aryls exhibit little electronic bias (e.g. Ph vs 4-F-C_6H_4), both diastereomeric precursors underwent dyotropic reactions through the sterically

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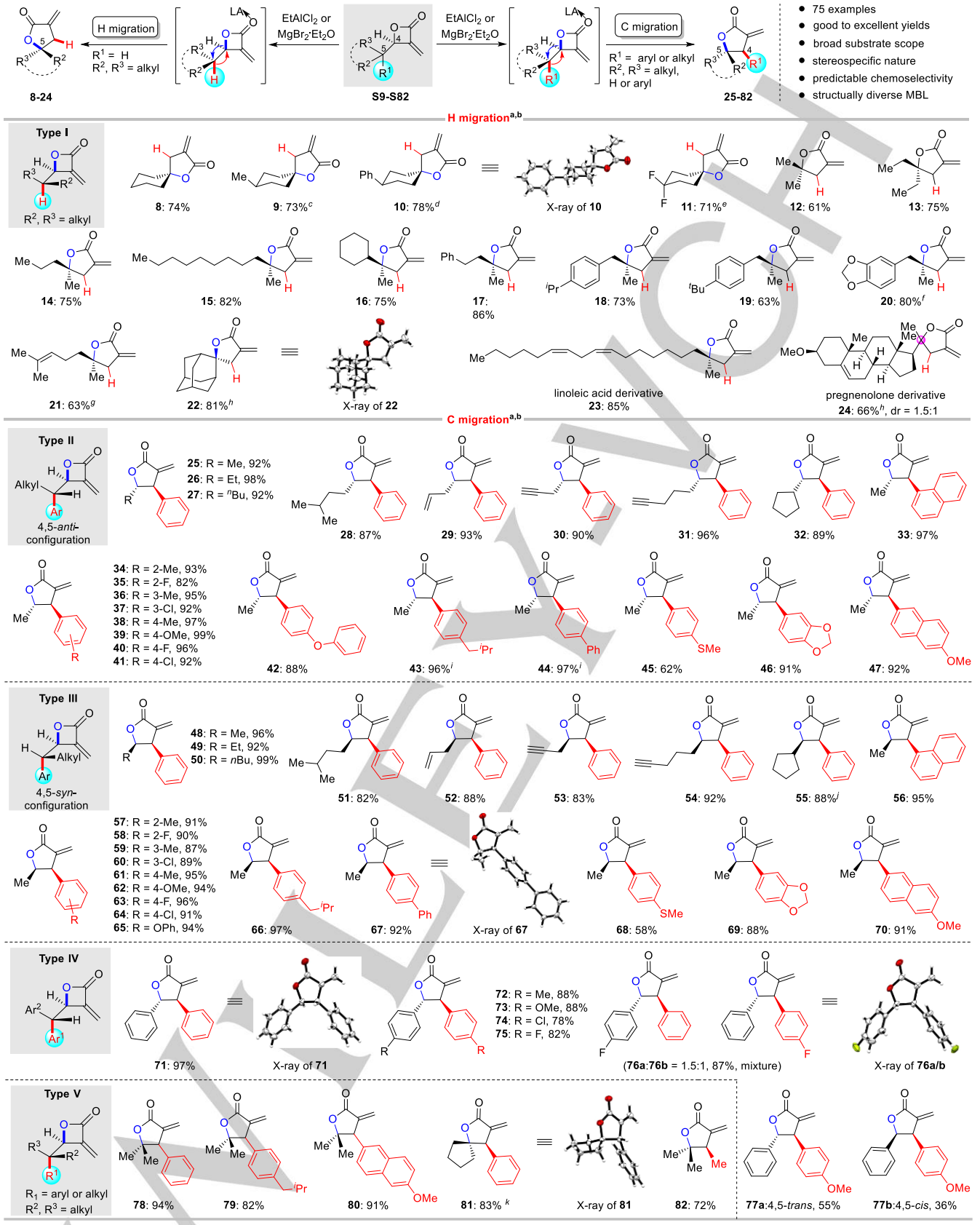

Figure 3 Dyotropic rearrangements of α-methylene-β-lactones bearing different substituents at the C5 position. [a]Otherwise noted, the reactions were conducted with a standard protocol: α-methylene-β-lactones (0.20 mmol, 0.05M), $EtAlCl_2$ (1.1 equiv.) in Et_2O (4.0 mL) at RT for 20 min. [b] Isolated yield. [c] 50 min. [d] 90 min. [e] $MgBr_2{\cdot}Et_2O$, RT, 20 min. [f] 120 min. [g] 60 min. [h] 40 min. [i] gram-scale synthesis. [j] 30 min. [k] 10 min.

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favorable transition states as mentioned above, thus resulting in a mixture of 4,5-*trans*-MBL **76a** and **76b** through Ph- and 4-F-C_6H_4 migration, respectively. Of note, **76a**/**76b** could not be separated by chromatographic method, and their identities were determined by analogy to the well-established compounds.[24] In contrast, for substrates having two electronically biased aryls (e.g. Ph vs 4-MeO-C_6H_4), 4,5-*trans*- (**77a**) and 4,5-*cis* products (**77b**) were isolated in 55% and 36%yields, respectively. Obviously, due to its strong electronic donating nature, 4-MeO-C_6H_4 migrates preferentially for both diastereomeric precursors, even though the reaction leading to **77b** would adopt a sterically unfavorable transition state. Lastly, α-methylene-β-lactones bearing an all-carbon quaternary carbon at C-5 position (type V) also proved be suitable substrates. As expected, aryl migration occurred for the substrates bearing one aryl and two alkyls (e.g. **78**-**81**); comparably, alkyl migration took place in the absence of aryl at C-5 position (e.g. **82**).

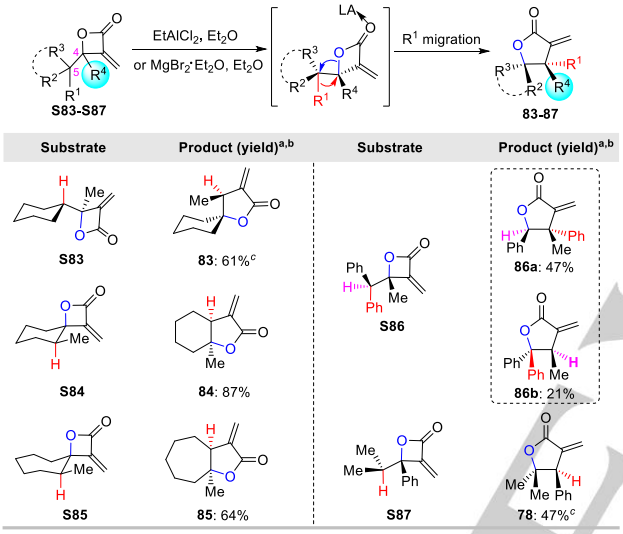

Figure 4 Scope of α-methylene-β-lactones bearing different substituents at C4 position. [a]Otherwise noted, the reaction was conducted with α-methylene-β-lactones (0.20 mmol, 0.05M), $EtAlCl_2$ (1.1 equiv.) in Et_2O (4.0 mL) at RT for 20 min. [b] Isolated yield. [c] $MgBr_2{\cdot}Et_2O$, RT, 1 h.

Having explored the structural variants at C-5 positions, we sought to expand the reaction to some more challenging substrates (Figure 4). First, α-methylene-β-lactones bearing a quaternary carbon at C-4 position were evaluated. Theoretically, this type of substrates readily undergoes ring-cleavage through E1-type elimination.[10b] To our delight, the dyotropic rearrangements of this kind of substrates could be achieved under the judiciously selected conditions. For example, both substrates **S84** and **S85** underwent dyotropic reactions smoothly in the presence of $EtAlCl_2$; comparably, the reaction of **S83** had to be conducted with $MgBr_2{\bullet}Et_2O$ as promoter. Notably, both **84** and **85** share considerable similarity to the core skeletons of various natural products (e.g. eriolangin and helenalin), which paves the way to their application in natural product synthesis. Another interesting case was the reaction of 4-methyl-5,5-diphenyl-α-methylene-β-lactone (**S86**), wherein both aryl- (**86a**) and hydrogen-migration (**86b**) products were obtained. Obviously, the introduction of a methyl group on the C4 position partially inverts the migratory sequence of aryl and hydrogen, presumably as a result of the interplay of electronic and steric effect. On one hand, with the C4-O1 bond located at a tertiary carbon, the reaction may proceed, at least in part, through a stepwise mechanism involving an allylic tertiary carbocation intermediate. Thus, hydrogen migration takes place preferentially due to the engagement of a more stable diphenyl-substituted carbocation species.[25] On the other hand, even a concerted mechanism is possible in this case, aryl migration would be inhibited to some extent, owing to the increasing steric hindrance between the migrating group and the C4 substituents. Finally, we found that introducing an aryl onto the C-4 position further increased the tendency of underlying E1-elimination pathway. Indeed, the reaction of **S87** only led to the desired product (**78**) in a moderate yield, together with substantial amounts of elimination product (not shown).

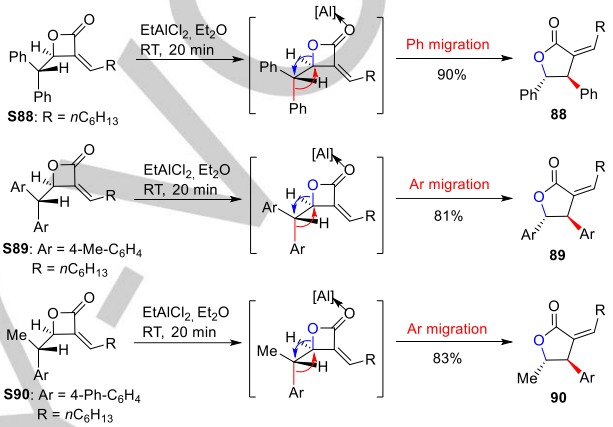

Figure 5 Dyotropic rearrangements of α-alkylidene-β-lactones

Besides α-methylene-γ-butyrolactones, we envisioned that the dyotropic reaction developed by us could also be applied to the synthesis of α-alkylidene-γ-butyrolactones, another important structural motif found in natural products and drugs.[1c] As the proof-of-concept cases, α-alkylidene-β-lactones **S88**-**S90**, readily prepared from the corresponding α-methylene-β-lactones through cross metathesis reaction,[19] were evaluated under the optimal conditions. Gratifyingly, all of them underwent dyotropic reactions smoothly, giving rise to α-alkylidene-γ-butyrolactones **88**-**90** in high yields and selectivity (Figure 5).

Computational Study and Mechanistic Rationalization. Having fully explored the substrate scope of the dyotropic rearrangements of *α*-methylene-*β*-lactones, we then conducted a computational study to gain deep insight into the mechanisms of some representative reactions. Stationary points on the potential energy surface were located at PBE0-D3/def-TZVP level.[26] More accurate single point energies were calculated with double-hybrid functional at PWPB95-D3/def2-QZVPP level.[27] The solvent effect in Et_2O was evaluated with the SMD method.[28] All energies mentioned below are solvated Gibbs free energies. First, we studied the type I substrates using **6** as a model compound. Transition states (TSs) for both stepwise and concerted mechanisms are located (Figure 6a and Figure S1). For H-migration process towards product **8**, a concerted pathway through **TS1** is the favored mechanism with an activation Gibbs free energy of 86.4 kJ/mol. The geometry of **TS1** indicates that C-O breaking precedes C-H migration (Figure 6b). An intrinsic reaction coordinate (IRC) calculation starts from **TS1** also confirmed that the concerted process is highly asynchronous (Figure 6b). Judging from the bond lengths, this rearrangement

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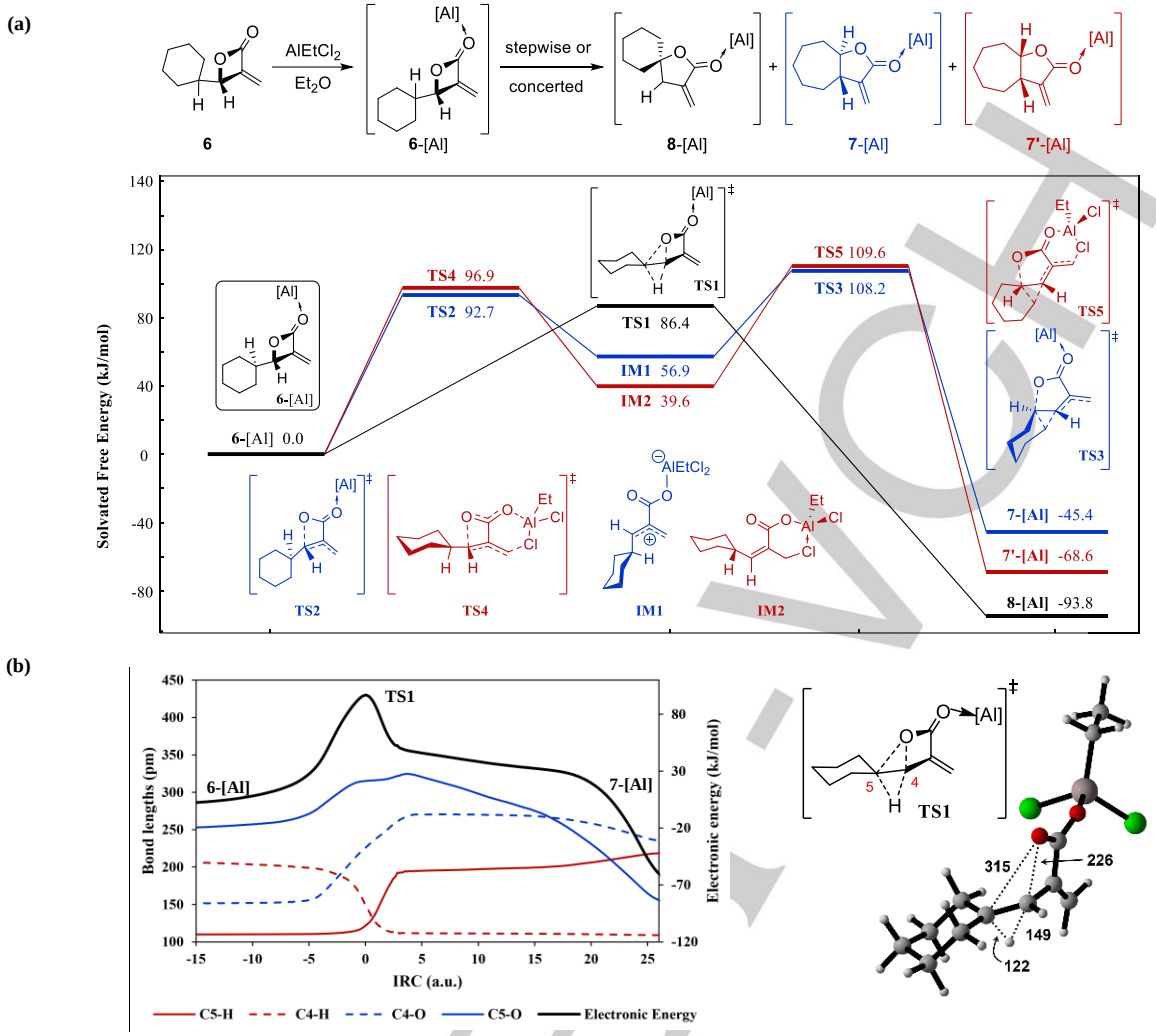

Figure 6 (a) Energy profile for the dyotropic reactions of **6** (bond lengths in pm). [Al] = $AlEtCl_2$. (b) Solvated electronic energies and selected bond lengths along the IRC of **TS1**, showing three asynchronous stages of the concerted dyotropic process. Bond lengths labelled in TS1 structure are in pm.

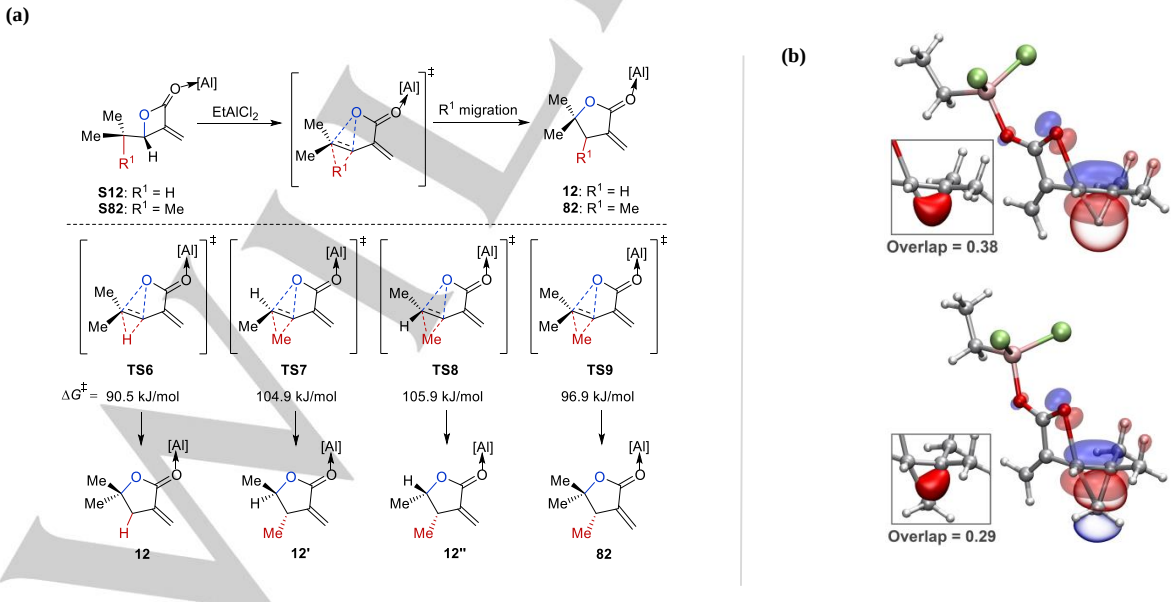

Figure 7 (a) Solvated activation Gibbs free energy for concerted reaction pathways of *i*Pr- and *t*Bu-substituted substrates. (b) SOMO isosurfaces (value = 0.07 a.u.) generated by biorthogonalization for the fragments and the isosurfaces (value = 0.015 a.u.) for the overlap between two orbitals (defined by the product of those orbitals

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reaction can be divided into three asynchronous stages: (1) C4-O1 breaking takes place; (2) C5-H breaking and C4-H formation happen synchronously; (3) C5-O1 bond formation occurs only after the above processes are finished. On the contrary, stepwise pathways were found favorable for the alkyl-migration processes. For the formation of 5/7-*cis*-fused byproduct **7′**, the optimal pathway goes through a CI-assisted mechanism (**TS4**, **IM2,** **TS5**), where **TS5** is the rate-determining state, giving a barrier of 109.6 kJ/mol, 23.2 kJ/mol higher than that of H migration. As for 5/7-*trans*-fused byproduct **7**, a stepwise pathway via **TS2**, **IM1**, **TS3** is located. The migration/lactone formation transition state **TS3** is the rate-determine state, with a barrier of 108.2 kJ/mol, which is 21.8 kJ/mol higher than that of H-migration. We also located several other pathways leading to product **8**, **7** and **7′**, which is discussed in the Supporting Information.

To investigate the reason behind the preference of H migration over alkyl migration, we compared the reaction selectivity of *i*Pr- (**S12**) and *t*Bu-substituted (**S82**) substrates (Figure 7a). The difference of activation Gibbs free energy ($\Delta\Delta G^{\ddagger}$) between H-migration (**TS6**) and Me-migration (**TS7** and **TS8**) is about 15 kJ/mol, making H migration the favorable pathway. To semiquantitatively decouple these two effects, we could use **TS9** as a reference. The difference of orbital interaction between the migration group and the rest of the molecule could be estimated by comparing **TS6** and **TS9**, which accounts for about 6.5 kJ/mol. For the difference in the stabilization of the partial carbocation, we could compare **TS7**/**TS8** with **TS9**, which accounts for *ca.* 8.5 kJ/mol difference. These comparison shows that carbocation stabilization and orbital interaction have a similar level of contribution to the tendency of H-migration over alkyl-migration. To illustrate the orbital overlap in the transition state structures, wavefunction analysis was performed.[29] In Figure 7b, the transition states were fragmented into the migrating H or alkyl groups and the rest of the molecule. SOMOs generated by biorthogonalization for both fragments and the overlap is shown. It shows better orbital interaction for H migration than that of Me migration.

For substrates that have aryl substitution at C-5 position, we need to understand the preference of aryl migration over H or alkyl migration. Dyotropic rearrangement of the substrate **S25** was chosen as a model reaction, wherein Ph-, H-, and Me-migration pathways are located (Figure 8a). For Ph migration, two pathways were found to have almost the same activation Gibbs free energy of 83.6 kJ/mol, between which one is concerted (through **TS10**), and the other has a shallow phenonium ion intermediate (**IM3**). In the concerted pathway, a flat area can be seen on the IRC path after the transition state (Figure 8b, c.a. 5-25 a.u.), which also corresponds to a similar structure that C5-Ar exists intermediary state between bonding and non-bonding scenario. These observations indicate that the delocalization of such carbocation strongly stabilizes the transition-state-like structure, thus lowering the overall activation Gibbs free energy. On the contrary, the pathways for H migration and Me migration have an activation Gibbs free energy of 100.1 kJ/mol (**TS15**) and 121.0 kJ/mol (**TS13**, **IM4**, **TS14**), respectively. Interestingly, the optimal pathway for Me-migration involves a shallow minimum **IM4** with the C-H bond stabilizing the generated partial carbocation.

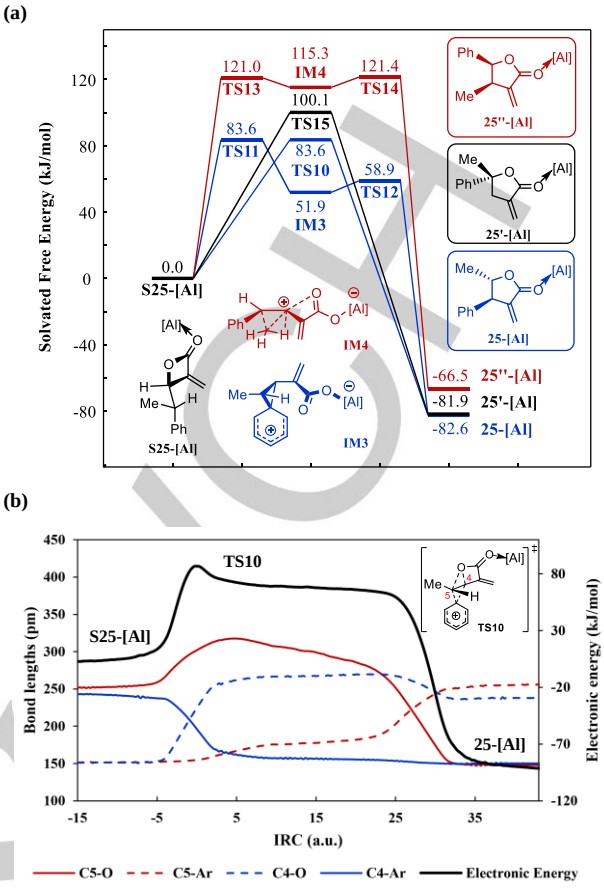

Figure 8 (a) Energy profile for the dyotropic reactions of aryl-substituted substrate. (b) Energy and selected bond lengths for concerted Ph migration along the IRC of **TS10**.

Synthetic Application. Several striking features of the newly developed dyotropic reaction, including excellent efficiency, broad substrate scope and high stereospecificity, render it an appealing tool for accessing MBL-containing natural products and pharmaceutical agents.

We first applied the present dyotropic rearrangement to the preparation of enantiomerically enriched MBL. As shown in Figure 9a, the enantiopure α-methylene-β-lactone **S91** (for its preparation, see SI) underwent dyotropic reaction smoothly, giving rise to the chiral 5,5-disubstituted MBL **91** with high efficiency (75%). A slight erosion of ee value (99%→85% ee) was observed, indicating that both asynchronous concerted and stepwise mechanisms coexisted in the reaction. This result was in good agreement with our calculation study.

Next, several natural product-relevant scaffolds were prepared based on the newly developed chemistry (Figure 9b). For example, the 6/5-fused bicyclic MBL **92a/92b** (*trans:cis* = 3.2:1), a key structural element in various natural products such as santamarine,[30] was obtained from cyclopentyl substituted α-methylene-β-lactone **S92** in 54% yield, together with small amounts of 5/5 bicyclic spiro product **92c** (17%). Notably, different from the substrate **6**, C-C bond migration took place predominantly in this case, likely attributed to that cyclopentane has a higher ring-strain energy (RSE) than cyclohexane,[31] and thus it is easier to undergo ring expansion through alkyl migration. Besides, the 6/7/5 tricyclic MBL **93** was also prepared from the corresponding precursor (**S93**) through dyotropic rearrangement involving aryl migration.

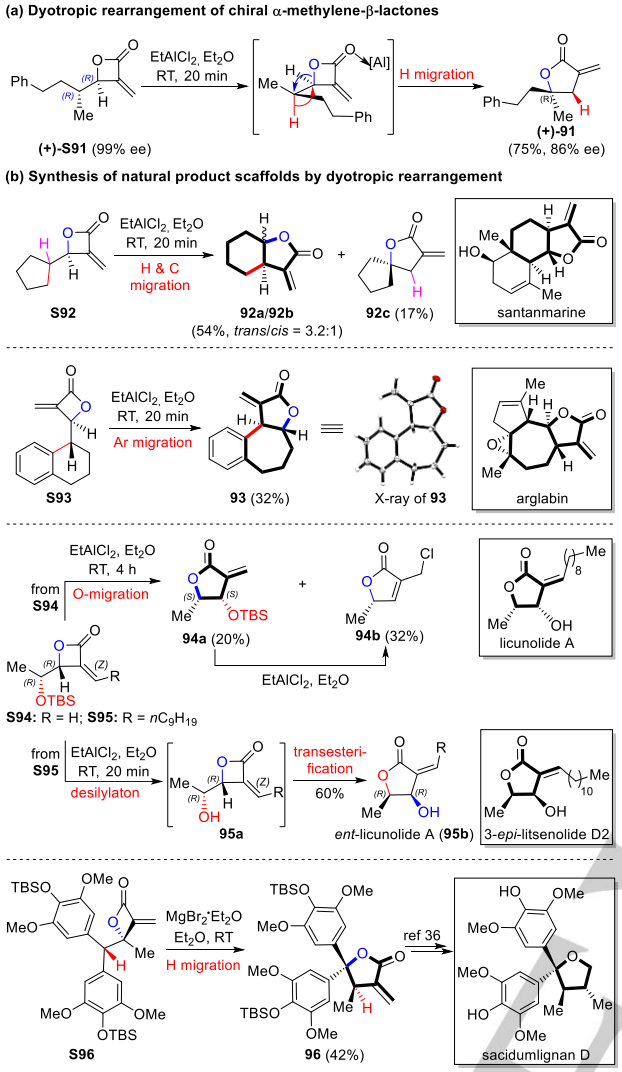

Figure 9 Synthetic application. (a) Synthesis of enantioenriched MBL. (b) Synthesis of natural product-relevant MBL.

Sharing considerable structural similarity with the well-known tricyclic sesquiterpenoids such as arglabin, **93** could serve as a natural product mimic in biomedical research.

3-Hydroxyl-α-methylene-γ-butyrolactone features the core skeleton of a unique family of natural products as represented by licunolide A.[32] We envisioned that this class of natural products could be accessed through dyotropic rearrangement involving C-O migration. To test this idea, the chiral α-methylene-β-lactone **94** (for its preparation, see SI) was examined under the standard conditions. It turned out that the dyotropic reaction did work. However, the resulting O-migration product (**94a**) was unstable and readily advanced to 2(5H)-furanone derivative **94b** through a Cl^--initiated S_N2' substitution reaction. Carefully controlling the reaction time allowed for the isolation of **94a** and **94b** in 20% and 32% yields, respectively. In parallel, α-alkylidene-β-butyrolactone **S95** was also explored. To our disappointment, this substrate failed to deliver the expected dyotropic rearrangement product. Instead, *ent*-licunolide A (**95b**)[33] was obtained as major product, apparently through the deprotection of TBS group followed by intramolecular transesterification reaction.[13,34] Of note, the absolute stereochemistry of **95b** is identical to another natural product 3-*epi*-litsenolide D2.[32]

Lastly, a formal synthesis of sacidumlignan D[35] was completed based on a H-migration dyotropic reaction. As shown, 5,5-diaryl-4-methyl substituted α-methylene-β-lactone **S96**, upon treatment with $MgBr_2$•Et_2O in Et_2O, underwent dyotropic rearrangement smoothly, providing the 5,5-diaryl-4-methyl substituted MBL **96** as a major product. Of note, a small amount of aryl-migration product (structure not shown) was also detected in this case. Since compound **96** has been reported as a key synthetic intermediate *en route* to sacidumlignan D,[36] the present work provides a formal synthesis of this natural target.

Conclusion

In summary, an unprecedented dyotropic rearrangement of α-methylene-β-lactones has been developed, the key essences of which include: (1) α-methylene-β-lactone, a highly strained small ring system notorious for its fragile nature, has been successfully introduced to dyotropic rearrangements for the first time; (2) a unique reaction system ($EtAlCl_2$-Et_2O) has been identified, which warrants the new variant of dyotropic reactions proceed with high efficiency and chemoselectivity; (3) a broad range of α-methylene-γ-lactones displaying remarkable structural diversity have been accessed in a finely controllable manner, which could not be readily achieved by the conventional methods; (4) distinct from the previously reported dyotropic reactions, the present one most likely proceeds through an asynchronous concerted or a stepwise mechanism. Taking together, this work not only enriches the repertoire of dyotropic rearrangements, but also offers a powerful tool for the synthesis of MBL-containing compounds. We anticipate that it will find widespread application in organic synthesis and medicinal chemistry. Particularly, many of the obtained BML-containing compounds in this work are closely relevant to bioactive natural products and pharmaceutical agents, which hold a great promise to serve as leads or chemical tools in biomedical research. Actually, we have found that a number of the products obtained in this study displayed significant cytotoxicity against a panel of cancer cells, with IC_{50} ranging from 1-10 μM (for details, see SI). We are now working on the identification of their biological targets. Meanwhile, we are also striving to apply the present methodology to the total synthesis of complex natural products, and related work will be communicated in due course.

Acknowledgements

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Keywords: dyotropic rearrangement • β-lactone • γ-butyrolactone • ring expansion • natural product

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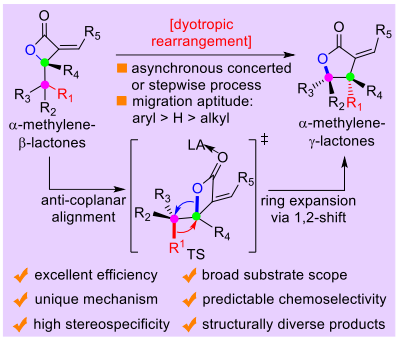
RESEARCH ARTICLE

Entry for the Table of Contents

An unprecedented dyotropic rearrangement of α-methylene-β-lactones has been realized, which provides an enabling tool for the synthesis of various structurally diverse α-methylene-γ-butyrolactones. Distinct from conventional dyotropic rearrangements, the present reactions proceed through either an asynchronous concerted or a stepwise mechanism.



Xiaoqiang Lei, Yuanhe Li, Yang Lai, Shengkun Hu, Chen Qi, Gelin Wang, and Yefeng Tang**

Page No. – Page No.

Strain-Driven Dyotropic Rearrangement: A Unified Ring-Expansion Approach to α-Methylene-γ-butyrolactones